

Statistical Analysis Plan

Protocol Title:	A Phase 3 Japanese Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention	
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Original (v1.0)	23SEP2019	NA
Amendment 1 (v2.0)	15APR2020	<ul style="list-style-type: none"> • Table 5-1 updated to clarify the source data corresponding to the week 32/48 visit date. • Section 7.1 updated to clarify the scope of the primary analysis will include efficacy and safety data during the DBTP only to be consistent with the planned analyses objectives. • Table 9-1, Table 9-2, and Section 9.5 updated to include an additional sensitivity analysis to examine the homogeneity across treatment-by-stratification factors with respect to the primary and secondary endpoints. • Section 9.6.2 updated to <ul style="list-style-type: none"> ○ Include device-related AEs ○ Clarify broad search for Alopecias AMQ EOI ○ Clarify the threshold of at least 3% for identifying most frequent TEAEs. • Section 9.6.7 added to clarify BDI-II analysis. • Section 12 updated to clarify the scope of this Statistical Analysis Plan will not include the optional interview-based substudy per Protocol Amendment 2. • Editorial/changes were made throughout the document to improve overall clarity.
[Amendment 2 (v3.0)]		

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
AHM	Acute Headache Medication
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMQ	Amgen Medical Query
AMSM	Acute Migraine-specific Medication
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BDI	Beck Depression Inventory
BMI	Body Mass Index
CM	Chronic Migraine
CMH	Cochran Mantel Haenszel
COA	Clinical Outcome Assessment
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DBTP	Double-blind Treatment Period
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EM	Episodic Migraine
EOS	End of Study
ET	Early Termination
FAS	full analysis set
GSO-DM	Global Study Operations-Data Management
IP	Investigational Product
IPD	Important Protocol Deviation
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information

Abbreviation or Term	Definition/Explanation
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
LOCF	Last Observation Carried Forward
LSM	Least Squares Means
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MHD	Monthly headache days
MI	Multiple Imputation
MMD	Monthly Migraine Days
MNAR	Missing Not at Random
NCI	National Cancer Institute
NRI	Non-responder Imputation
OLAS	Open-label Analysis Set
OLTP	Open-label Treatment Period
PK	Pharmacokinetic
PRO	Patient-Reported Outcome
Q4W	Every 4 Weeks
QM	Once Monthly
QTc	QT interval corrected
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SMQ	Standardized MedDRA Queries
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20170609, AMG 334 (erenumab) dated 19 December 2018. The scope of this plan includes the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none">To evaluate the effect of erenumab compared to placebo on the change from baseline in mean monthly migraine days (MMD)	<ul style="list-style-type: none">Change from baseline in mean MMD over months 4, 5, and 6 of the double-blind treatment period (DBTP)
Primary Estimand	
<p>The primary estimand consists of:</p> <ul style="list-style-type: none">The target population, which is Japanese subjects diagnosed with migraine who were randomized, received at least one dose of investigational product, and had at least 1 change from baseline measurement in MMD during the DBTP.The primary endpoint, which is the change from baseline in mean MMD over months 4, 5, and 6 of the DBTP.The summary measure, which is the mean difference of the primary endpoint between AMG 334 70 mg and placebo groups.The intercurrent event, adherence to treatment will be ignored and the primary endpoint will be assessed for all subjects in the target population regardless of adherence to treatment.	
Secondary	
<ul style="list-style-type: none">To evaluate the effect of erenumab compared to placebo on the proportion of subjects with at least a 50% reduction from baseline in mean MMD	<ul style="list-style-type: none">Achievement of at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6 of the DBTP
<ul style="list-style-type: none">To evaluate the effect of erenumab compared to placebo on the change from baseline in mean monthly acute migraine-specific medication treatment days	<ul style="list-style-type: none">Change from baseline in mean monthly acute migraine-specific medication treatment days over months 4, 5, and 6 of the DBTP
Safety	
<ul style="list-style-type: none">To evaluate the safety and tolerability of erenumab	<ul style="list-style-type: none">Subject incidence of treatment-emergent adverse eventsClinical laboratory values and vital signsSubject incidence of anti-erenumab antibodies

Objectives	Endpoints
Exploratory	

Objectives	Endpoints
Exploratory (continued)	

1. *Journal of the American Medical Association*, 2001; 286: 2669-2674.

Objectives	Endpoints
Exploratory (continued)	

1. *Journal of the American Medical Association*, 1997; 277: 1001-1005.

2.2 Hypotheses and/or Estimations

The primary endpoint will be tested for erenumab 70 mg compared to placebo at a 2-sided significance level of 0.05:

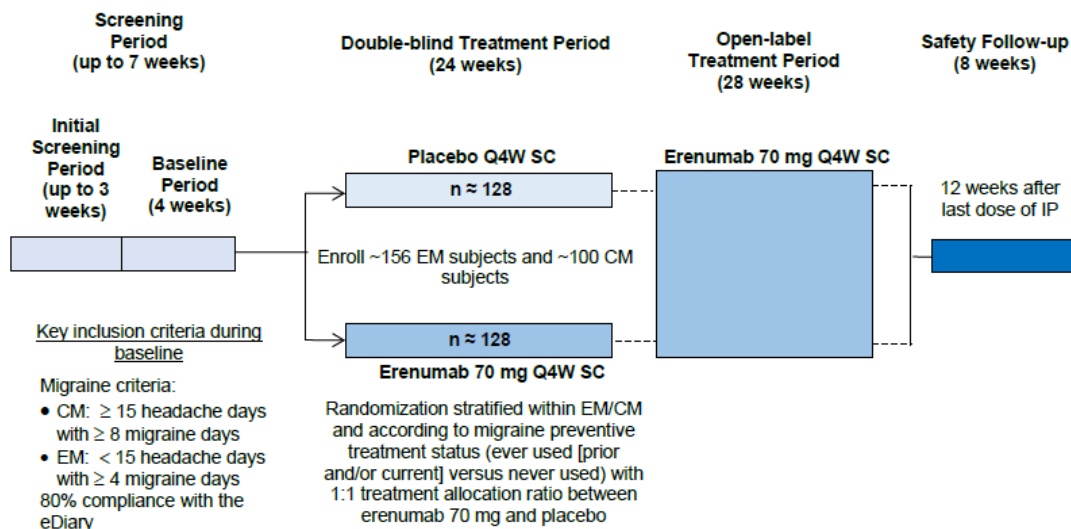
- Null Hypothesis: In subject with EM or CM, the erenumab 70 mg is same as placebo, in terms of the change from baseline in the mean monthly migraine days over months 4, 5, and 6
- Alternative Hypothesis: In subject with EM or CM, the erenumab 70 mg is different from placebo, in terms of the change from baseline in the mean monthly migraine days over months 4, 5, and 6

3. Study Overview

3.1 Study Design

This is a Phase 3, multicenter, randomized, stratified, double-blind, placebo-controlled, parallel-group study of subjects in Japan with EM or CM. The study is composed of an initial screening phase (up to 3 weeks), a 4-week baseline phase, a 24-week double-blind treatment period (DBTP), a 28-week open-label treatment period (OLTP), and an 8-week safety follow-up period (12 weeks after the last dose of investigational product). Subjects will have scheduled in-clinic study visits monthly from week -4 through the end of the OLTP.

The overall study design is described by the following study schema.



CM = chronic migraine; EM = episodic migraine; eDiary = electronic diary; IP = investigational product; Q4W = every 4 weeks; SC = subcutaneously.

3.1.1 Double-blind Treatment Period

Approximately 256 eligible subjects (including approximately 156 EM and 100 CM subjects) will be randomized in a 1:1 ratio to erenumab 70 mg or placebo (in each arm, approximately 78 subjects with EM and 50 subjects with CM). The randomization will be performed by IVRS/IWRS and subjects will be stratified by EM/CM and migraine preventive treatment status (ever used [prior and/or current] or never used). The enrollment limit on current migraine prophylactic medication users will be 25% of total EM subjects and 40% of total CM subjects.

Amgen investigational product (ie, erenumab 70 mg or placebo) will be dosed every 4 weeks (Q4W) by subcutaneous (SC) injections. Double-blind erenumab 70 mg or placebo will be administered during the 24-week DBTP (ie, at day 1 and weeks 4, 8, 12, 16, and 20).

Migraine and non-migraine headache outcomes and other efficacy measures will be assessed based on eDiary data.

Subjects who permanently discontinue investigational product during the DBTP are to continue to return for all other study procedures until the end of the DBTP.

3.1.2 Open-label Treatment Period

The 24-week DBTP is followed by a 28-week OLTP. Erenumab 70 mg will be dosed Q4W by SC injections. Open-label erenumab 70 mg will be administered during the 28-week OLTP (ie, at weeks 24, 28, 32, 36, 40, 44 and 48).

3.1.3 Safety Follow-up Period

Subjects who complete or discontinue investigational product will complete the safety follow-up visit 12 weeks after the last dose of investigational product.

3.2 Sample Size

The primary endpoint is the change from baseline in mean MMD over months 4, 5, and 6 of the DBTP.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The treatment effect and

variability are weighted based on treatment effect and variability estimates from Japanese EM Study 20120309 and pivotal global CM Study 20120295. Randomizing

256 subjects (128 subjects per treatment group, approximately 78 for EM and 50 for CM) will account for 10% dropout.

Furthermore, simulation of erenumab data shows that the probability of achieving the point estimate of treatment difference between erenumab and placebo

(erenumab – placebo) < -1 MMD is [REDACTED]

respectively (a ≥ 1 MMD reduction has been found clinically meaningful

[Silberstein et al, 2010]). The joint probability of demonstrating statistical significance in the overall population and achieving the point estimate of treatment difference between erenumab and placebo < -1 MMD in both EM and CM subpopulations is 80% (Table 3-1).

Table 3-1. Likelihood of Observing Greater MMD Reduction in Erenumab 70 mg Compared to Placebo Overall and in the EM/CM Subgroups

	Sample Size ^a	
	140 EM Subjects (70 per group)	90 CM Subjects (45 per group)
1. Power for achieving statistical significance for the primary endpoint in overall population ^b	[REDACTED]	
2. Probability of achieving point estimate of treatment difference erenumab vs placebo < -1 MMD ^c	[REDACTED]	[REDACTED]
Joint probability of achieving both criteria above ^c	[REDACTED]	

CM = chronic migraine; EM = episodic migraine; MMD = monthly migraine days

^a Not including 10% dropouts

^b Based on the weighted average with the respective sample size of EM/CM subgroup, treatment difference (vs placebo) in overall population was estimated to be [REDACTED]

4. Covariates and Subgroups

4.1 Planned Covariates

All analyses of efficacy endpoints will be adjusted for the effect of the stratification factors, including EM/CM and migraine preventive treatment status (ever used [prior and/or current] or never used), and the baseline value of the efficacy endpoint of interest (eg, baseline monthly migraine days will be added in the model as a covariate for the endpoint of change from baseline in monthly migraine days). Stratification factors based on randomization will be included in the model.

4.2 Subgroups

The primary, secondary efficacy, and selected safety endpoints will be analyzed in the subgroups defined by the stratification factors (EM vs CM, and migraine preventive treatment status [ever used [prior and/or current] vs never used]) as well as prior migraine preventive treatment failure status (failed vs not failed [including never used]), BMI (< median vs \geq median), and body weight (< median vs \geq median). Stratification factors based on actual data will be used for the subgroup analyses.

The subgroups will be re-examined for appropriateness and may be re-categorized (due to small sample size, for example, if there are < 10% of subjects within a subgroup) before unblinding.

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Efficacy Endpoints Based on Daily eDiary Collection

Acute Headache Medication (AHM)

Acute headache medications include

- Triptan-based migraine medications
- Ergotamine-based migraine medications
- Non-opioid acute headache medications
- Non-opioid butalbital containing medications
- Opioid-containing acute headache medications
- Opioid-containing butalbital containing medications

Acute Migraine-specific Medication (AMSM)

A subset of acute headache medication consisting of triptan-based migraine medications and ergotamine-based migraine medications

Qualified Headache

A qualified headache is defined as

- A headache of duration \geq 4 hours, or
- A headache of duration < 4 hours during which an acute headache medication is administered

Headache Day

A calendar day (00:00 to 23:59) in which the subject experiences \geq 1 qualified headache or takes \geq 1 acute migraine-specific medication to treat aura

Headache Pain Intensity

Worst or peak pain intensity collected on a headache episode ranges from 1 to 10 with a higher score indicating more severe pain. Pain intensity are categorized into mild (1 to 3), moderate (4 to 6), and severe (7 to 10).

Qualified Migraine Headache

A qualified migraine headache is defined as

- A headache lasting for ≥ 4 hours, and meeting ≥ 1 of the following criteria (a and/or b):
 - a) ≥ 2 of the following pain features:
 - Unilateral
 - Throbbing
 - Moderate to severe (ie, headache pain intensity ≥ 4)
 - Exacerbated with exercise/physical activity
 - b) ≥ 1 of the following associated symptoms:
 - Nausea
 - Vomiting
 - Photophobia and phonophobia
- A headache during which an acute migraine-specific medication is administered regardless of the headache duration, pain features, and associated symptoms

Migraine Day

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified migraine headache or takes ≥ 1 acute migraine-specific medication to treat aura

Migraine Day With Moderate or Severe Pain Intensity

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified migraine headache with the worse or peak pain intensity of ≥ 4

Migraine Pain Intensity

Worst or peak pain intensity collected on a qualified migraine headache ranges from 1 to 10 with a higher score indicating more severe pain.

Acute Headache Medication Day

A calendar day (00:00 to 23:59) in which the subject takes ≥ 1 acute headache medication

Acute Migraine-specific Medication Day

A calendar day (00:00 to 23:59) in which the subject takes ≥ 1 acute migraine-specific medication

Diary Day

A calendar day (00:00 to 23:59) with complete headache, aura, and acute headache medication data recorded in the eDiary device

Information Day

A calendar day (00:00 to 23:59) which is either a headache day or a diary day

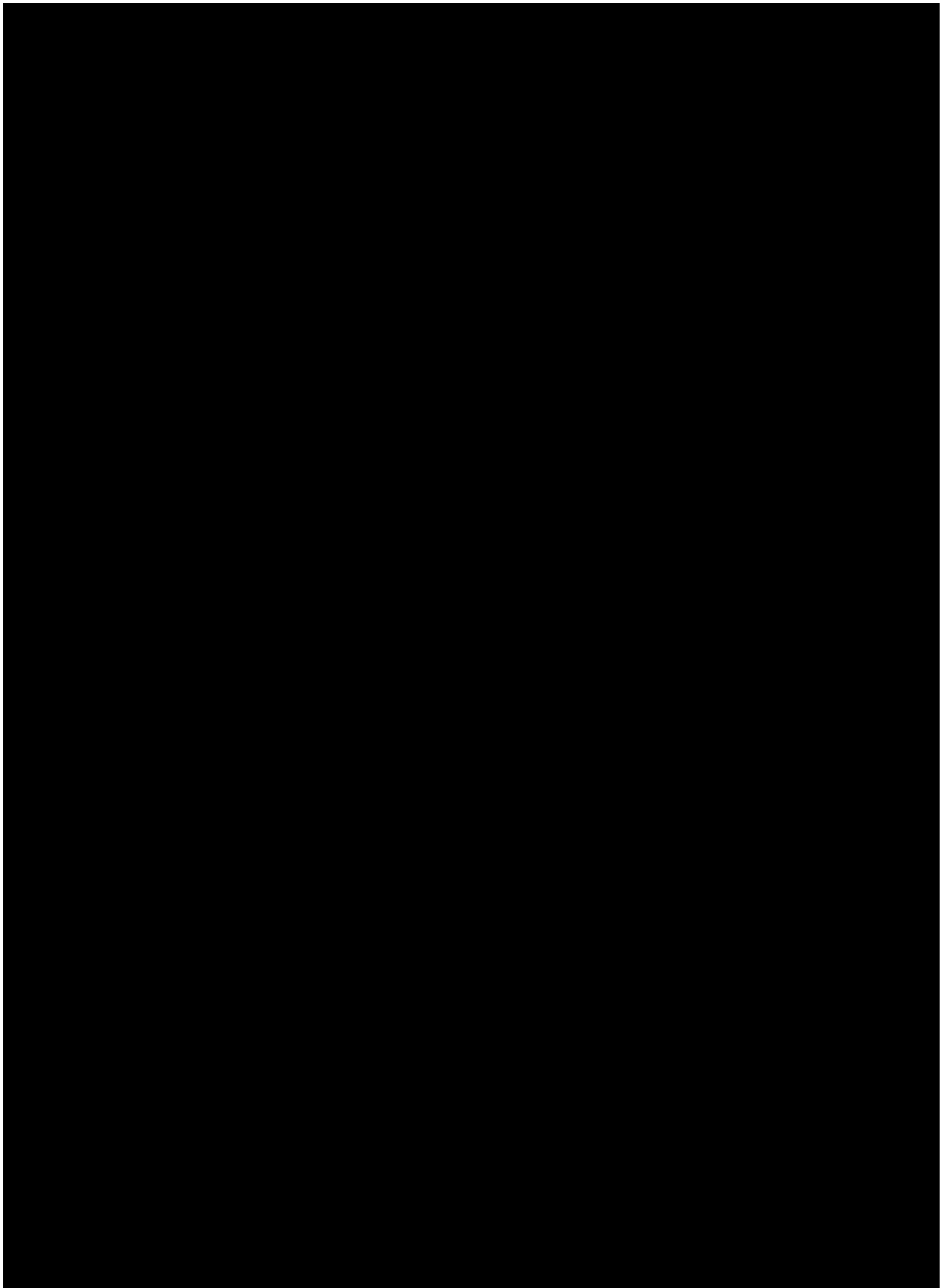
Monthly Frequency Variable in Days

Number of days of interest during one monthly interval as defined in [Table 5-1](#). Monthly frequency variables include

- Monthly migraine days (MMD)
- Monthly headache days (MHD)
- Monthly acute migraine-specific medication days

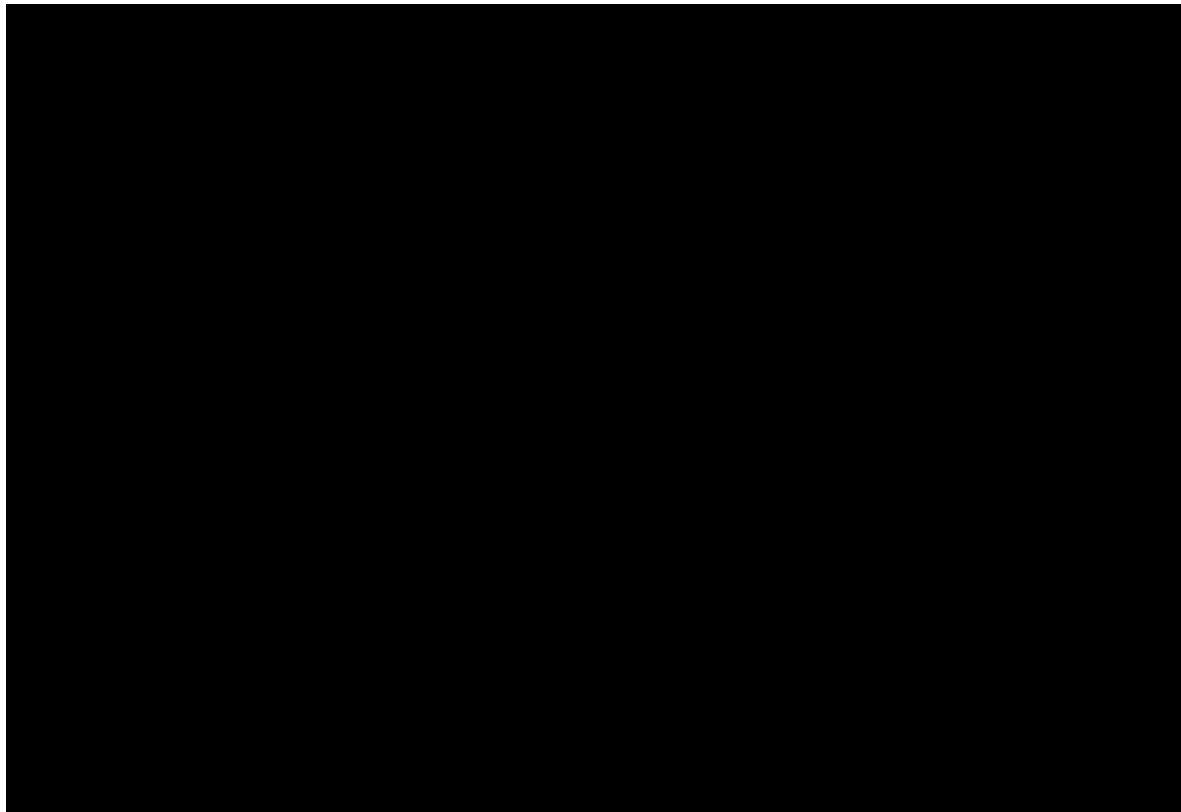
The following proration rule will be applied to all monthly frequency variables for each monthly interval.

Within Each Monthly Interval	Monthly Frequency Variable
≥ 14 diary days	Prorate to 28-day equivalent without rounding $\frac{\text{Number of frequency days within each monthly interval}}{\text{Number of information days within each monthly interval}} \times 28$
< 14 diary days	Set to missing





5.1.2 Efficacy Endpoints Based on Monthly Collection



5.1.3 Safety Endpoints

Serious Adverse Event (SAE)

An event categorized as “Adverse Event” with the indicator flag “Serious” equal to “Yes” on the Events eCRF starting on or after signing of the informed consent and up to the End of Study date

Treatment-emergent Adverse Event (TEAE)

An event categorized as “Adverse Event” on the Events eCRF starting on or after first dose of investigational product, as determined by “Did event start before first dose of investigational product” equal to “No” or missing, and up to the End of Study date

Serious Treatment-emergent Adverse Event

A treatment-emergent adverse event with the indicator flag “Serious” equal to “Yes” on the Events eCRF

Treatment-emergent Adverse Device Effect

A treatment-emergent adverse event with the indicator flag “Is there a reasonable possibility that the event may have been caused by the investigational device” equal to “Yes” on the Events eCRF

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician rating of suicidal behavior and ideation and consists of a maximum of 20 items to evaluate suicidal behavior and suicidal ideation.

Beck Depression Inventory (BDI)-II

The Beck Depression Inventory (BDI)-II is a 21-item questionnaire that assesses severity of depression. Each item is scored from 0 to 3. The total score is categorized into 4 severity grades: minimal depression (0 – 13), mild depression (14 – 19), moderate depression (20 – 28), and severe depression (29 – 63).

5.2 Study Dates

Informed Consent Date

The date on which subject signs the informed consent form.

eDiary Device Assignment Date

The date on which an eDiary device is assigned to a subject for the first time after completion of initial screening at week -4 visit.

Randomization (Enrollment) Date in DBTP

Randomization (Enrollment) Date in DBTP is the date on which a subject is assigned to one of the treatments through Interactive Voice Response System (IVRS) in DBTP.

First (DBTP) IP Dose Date

First (DBTP) IP Dose Date is the date on which a subject is administered the first dose of IP during the DBTP following randomization as recorded on the IP Administration eCRF. The first IP dose may be the same day or after the randomization date.

Last DBTP IP Dose Date

Last DBTP IP Dose Date is the date on which a subject is administered the last dose of IP during the DBTP as recorded on the IP Administration eCRF.

First OLTP IP Dose Date

First OLTP IP Dose Date is the date on which a subject is administered the first dose of IP during OLTP following completion of the DBTP as recorded on the IP Administration eCRF.

Last OLTP IP Dose Date

Last OLTP IP Dose Date is the date on which a subject is administered the last dose of IP during the OLTP as recorded on the IP Administration eCRF.

Last IP Dose Date

Last IP Dose Date is the date on which a subject is administered the last dose of IP, which can be during the DBTP or OLTP, as recorded on the IP Administration eCRF.

End of Study (EOS) Date

End of study (EOS) date is defined as the last date on which the subject participates in the study as recorded on the End of Study eCRF.

5.3 Study Points of Reference

Baseline Assessment

Baseline assessment for the endpoint of the interest is defined as the last non-missing measurement taken or the monthly interval assessed (for endpoints derived from daily eDiary collection) before the first dose of investigational product. In cases where baseline measurements are taken on the same day as IP, it will be assumed that these measurements are taken prior to IP being administered. For subjects who are randomized but not dosed after the randomization, the baseline of the study is defined as the last non-missing measurement prior to or on the date of randomization.

Only C-SSRS collected at Day 1 visit can be used as baseline. The entire set of ECG data from the Day 1 visit will be used as baseline. If the ECG was missing on Day 1, the entire set of ECG data from the screening visit will be used as baseline.

Pre-OLTP Baseline

Pre-OLTP baseline for the endpoint of interest is defined as the last non-missing measurement taken or the last monthly interval assessed (for endpoints derived from

daily eDiary collection) before the first dose of OLTP IP. In cases where the measurements are taken on the same day as the first dose of OLTP IP, it will be assumed that these measurements are taken prior to IP being administered.

Study Day 1

Study Day 1 is defined as the first IP dose date. For subjects who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization.

Study Day

Study Day is defined as the number of days from Study Day 1.

Before Study Day 1:

$$\text{Study Day} = (\text{Date of Interest} - \text{Date of Study Day 1})$$

On or after Study Day 1:

$$\text{Study Day} = (\text{Date of Interest} - \text{Date of Study Day 1}) + 1$$

Therefore, the study day prior to Study Day 1 is -1.

5.4 Study Time Intervals

5.4.1 Study Periods

The following data will be categorized into treatment periods. Any data occurred after EOS date will not be included in the analysis except for antibody data.

Efficacy, Laboratory, Antibody, ECG Diagnosis, C-SSRS

- DBTP: Study Day 1 to minimum (first OL dose date, EOS date)
- OLTP: (First OL dose date + 1) to EOS date

Adverse Events, Concomitant Medications

- DBTP: Study Day 1 to minimum (first OL dose date – 1, EOS date)
- OLTP: First OL dose date to EOS date

5.4.2 Monthly Intervals for Efficacy Endpoints Derived From Daily Diary Collection

The (4-week) monthly intervals for efficacy endpoints derived from daily eDiary collection will be determined based on each subject's monthly IP dosing dates. When an IP is missed, discontinued, or no longer required, a 28-day monthly interval will be used. Any eDiary data occurring after EOS date will not be included in the analysis.

Applicable efficacy endpoints utilizing the monthly intervals in [Table 5-1](#) include:

- Monthly migraine days (MMD)
- Monthly headache days (MHD)
- Monthly acute migraine-specific medication days

Table 5-1. Monthly Intervals for Efficacy Endpoints Derived From Daily Diary Collection

Study Period	Assessment Timepoint	Monthly Interval	
		Start Date (Day) ^a	End Date (Day) ^b
Baseline Period	Baseline	Device assignment date	Day prior to study day 1
Double-blind Treatment Period	Week 4 (Month 1)	Study Day 1	Week 4 dose date – 1
	Week 8 (Month 2)	Week 4 dose date	Week 8 dose date – 1
	Week 12 (Month 3)	Week 8 dose date	Week 12 dose date – 1
	Week 16 (Month 4)	Week 12 dose date	Week 16 dose date – 1
	Week 20 (Month 5)	Week 16 dose date	Week 20 dose date – 1
	Week 24 (Month 6)	Week 20 dose date	Week 24 dose date – 1
Open-label Treatment Period	Week 36 (Month 9)	Week 32 visit date ^c	Start date (day) + 27
	Week 52 (Month 13)	Week 48 visit date ^c	Start date (day) + 27

^a Start Date (Day) = End date (day) of previous monthly interval + 1 if IP dose date is not available

^b End Date (Day) = Start date (day) of current monthly interval + 27 if IP dose date is not available

^c eDiary will be re-activated at week 32 and week 48 visits during OLTP. **Week 32/48 visit date will be determined by week 32/48 dose date. If week 32/48 dose date is missing, week 32/48 vital signs assessment date will be used instead.**

5.4.3 Analysis Visits for Endpoints Based on Monthly Collection

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date except for safety follow-up is mapped to the analysis visit as in [Table 5-2](#) to [Table 5-6](#).

By-visit data collected on or before the first OLTP dose date belong to DBTP. Data collected after the first OLTP dose date, not including the safety follow-up visit, belong to OLTP. By-visit data collected on the safety follow-up visit do not belong to either treatment period and will not be categorized into analysis visits. Any data occurred after EOS date will not be included in the analysis except antibody data.

For by-visit summaries, if more than one visit with non-missing measurement (including the unscheduled visits, ie, CPEVENT = 'UNSCHED') fall within the same visit window, the following rules will be applied according to the order described below for selecting one visit per visit window for summary:

1. Scheduled visit will be used regardless of the distance from the target day. Unscheduled visit will only be used when there is no measurement from scheduled visit in the visit window.
2. The visit closest to the target day among visits of the same type (all scheduled visits or all unscheduled visits) will be considered for analysis.
3. If two assessment dates are equidistant from the target date, the latter visit will be considered for analysis.

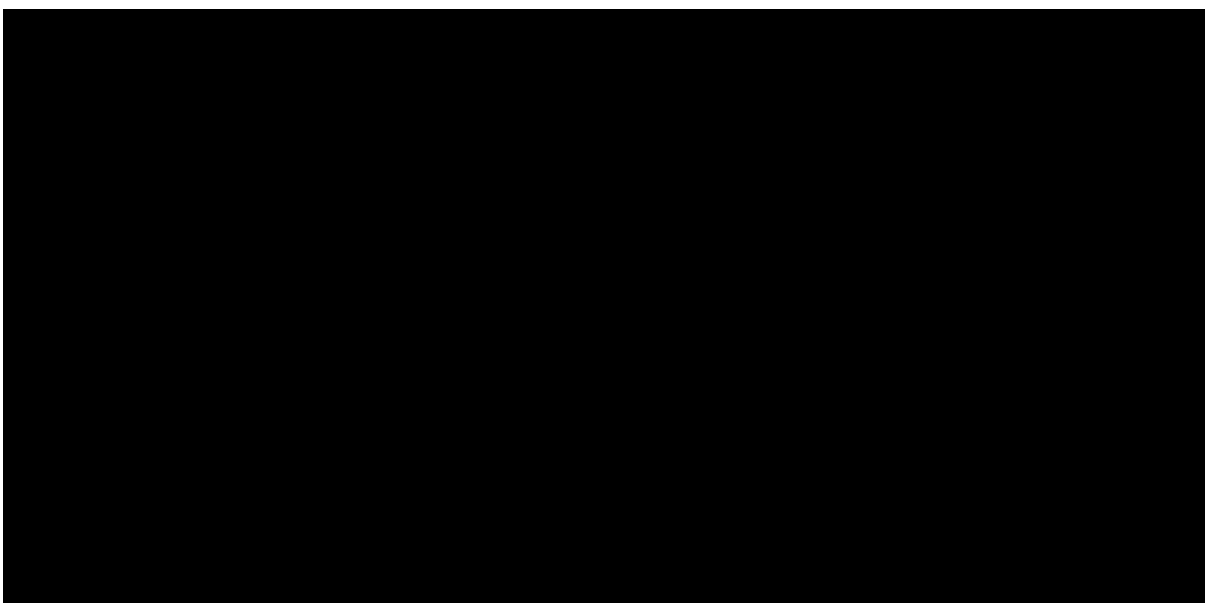


Table 5-3. Chemistry and Hematology Laboratory Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Double-blind Treatment Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
	Week 4 (Month 1)	29	16 to 43
	Week 12 (Month 3)	85	72 to 99
	Week 24 (Month 6)	169	156 to Week 24 dose date, if available, else to 183
Open-label Treatment Period	Week 52 (Month 13)	365	352 to 379
Safety follow-up	Data collected on the safety follow-up visit will not be categorized into analysis visit.		

Table 5-4. Vital Sign Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Double-blind Treatment Period	Day 1 (Baseline)	1	Last measurement \leq Day 1
	Week 4 (Month 1)	29	16 to 43
	Week 8 (Month 2)	57	44 to 71
	Week 12 (Month 3)	85	72 to 99
	Week 16 (Month 4)	113	100 to 127
	Week 20 (Month 5)	141	128 to 155
	Week 24 (Month 6)	169	156 to Week 24 dose date, if available, else to 183
Open-label Treatment Period	Week 28 (Month 7)	197	(Week 24 window end date + 1) to 211
	Week 32 (Month 8)	225	212 to 239
	Week 36 (Month 9)	253	240 to 267
	Week 40 (Month 10)	281	268 to 295
	Week 44 (Month 11)	309	296 to 323
	Week 48 (Month 12)	337	324 to 351
	Week 52 (Month 13)	365	352 to 379
Safety follow-up	Data collected on the safety follow-up visit will not be categorized into analysis visit.		

Table 5-5. Physical Measurement Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Double-blind Treatment Period	Day 1 (Baseline)	1	Last measurement \leq Day 1
	Week 24 (Month 6)	169	156 to Week 24 dose date, if available, else to 183
Open-label Treatment Period	Week 52 (Month 13)	365	352 to 379
Safety follow-up	Data collected on the safety follow-up visit will not be categorized into analysis visit window.		

Table 5-6. BDI-II Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Double-blind Treatment Period	Day 1 (Baseline)	1	Last measurement \leq Day 1
	Week 24 (Month 6)	169	156 to Week 24 dose date, if available, else to 183

5.5 Subject Disposition

Randomized

Individuals are considered randomized if they have been assigned a randomization number. Randomized individuals are referred to as “subjects”.

Exposed to Investigational Product

Subjects are defined as exposed if they receive at least one dose of investigational product.

Completing the Double-blind Investigational Product

Subjects are defined as completing double-blind investigational product if the primary reason for ending IP on End of IP DBTP eCRF is “Completed”.

Completing the Open-label Investigational Product

Subjects are defined as completing open-label investigational product if the primary reason for ending IP on End of IP OLTP eCRF is “Completed”.

Completing the Double-blind Treatment Period

Subjects are defined as completing the DBTP if they complete the week-24 assessment. It will be derived from the End of Double-Blind Treatment Phase eCRF with “Completed” as the primary reason for ending study phase.

Completing the Open-label Treatment Period

Subjects are defined as completing the OLTP if they complete the week-52 assessment. It will be derived from the End of Open-Label Treatment Phase eCRF with “Completed” as the primary reason for ending study phase.

Completing Study

Subjects are defined as completing study if they complete the entire 64 weeks of study evaluation. It will be derived from the End of Study eCRF with “Completed” as the primary reason for ending study.

On-study

Subjects are considered on-study if they have been randomized and have not yet had their EOS visit.

5.6 Arithmetic Calculations

Duration of Migraine

The number of years from the diagnosis date (DXDT) of migraine (migraine with aura or migraine without aura, whichever is earlier) to the date informed consent is signed.

Observed Portion	Missing Portion	Duration of Migraine (Years)
Year, Month, Day	NA	(Informed Consent Date – DXDT) / 365.25
Year, Month	Day	$\frac{[\text{Year}(\text{Informed Consent Date}) - \text{Year}(\text{DXDT})] + [\text{Month}(\text{Informed Consent Date}) - \text{Month}(\text{DXDT})]}{12}$ ^a
Year	Month, Day	$[\text{Year}(\text{Informed Consent Date}) - \text{Year}(\text{DXDT})]$ ^a

^a If it equals 0, add 1/12 years (ie, 1 month) to avoid a disease duration of 0.

Duration of DB IP Exposure

If subject enters into OLTP,

Minimum (Last DB Dose Date + 27, First OL Dose Date - 1, EOS Date) –
First DB Dose Date + 1

Otherwise, Minimum (Last DB Dose Date + 27, EOS Date) – First DB Dose Date + 1

Duration of OL IP Exposure

Minimum (Last OL Dose Date + 27, EOS Date) – First OL Dose Date + 1

Change From Baseline

Postbaseline monthly value – Baseline, as defined in [Section 5.4](#).

If the baseline or postbaseline value is missing, the change from baseline value will be set to missing.

Percent Change From Baseline

The change from baseline divided by baseline and multiplied by 100:

$$(\text{Postbaseline} - \text{Baseline}) * 100 / \text{Baseline}$$

If the baseline value is 0 and the postbaseline value is also 0, the percent change from baseline is set to 0. If the baseline value is 0 and the postbaseline value is non-zero, the percent change from baseline is set to missing.

Mean Monthly Change From Baseline Over Multiple Months

Arithmetic mean of the observed monthly change from baseline values for the months with non-missing change from baseline values

Subject Incidence

The subject incidence for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who enter that period (ie, number of at-risk subjects). For subjects with multiple occurrences of the same event in a given period, the event will only be counted once per subject in that period.

Exposure-adjusted Incidence Rate

The exposure-adjusted incidence rate for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event in a given period divided by total exposure time of all subjects who are at risk for the event. For subjects with a given event, only the time until the onset of each subject's first event contributes to the exposure time. For subjects without a given event, the exposure time is the entire duration of the period. This incidence rate will be presented as number of subjects per 100 subject-years.

5.7 Disease Characteristics

Treatment Failure of Prior Migraine Preventive Medications

Treatment failure of prior migraine prophylactic medications is determined by "Reason for ending medication" as "Lack of efficacy" or "Adverse Reaction" in the Prior Migraine Prophylactic Medication eCRF.

6. Analysis Sets

6.1 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received.

Tabulations of demographic and baseline characteristics, disposition, and important protocol deviations (IPD) will utilize this analysis set.

6.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) will be used to carry out the primary analyses of efficacy endpoints, which is a subset of the Full Analysis Set consisting of subjects who receive at least one dose of IP and have a baseline value and at least one post-baseline

value for the endpoint of the interest in the DBTP. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Analyses for efficacy endpoints during the DBTP will utilize this analysis set.

6.3 Safety Analysis Set

The Safety Analysis Set will consist of all randomized subjects who received at least one dose of IP. Subjects will be analyzed according to the randomized treatment unless a subject has received the incorrect dose during the entire DBTP. Analyses for safety endpoints and summary of IP administration in DBTP will utilize this analysis set.

6.4 Open-label Analysis Set

The Open-label Analysis Set (OLAS) will consist of all subjects receiving at least one dose of erenumab 70 mg in the OLTP. This analysis set will be used when summarizing data collected during the OLTP.

7. Planned Analyses

7.1 Primary Analysis

The objective of the primary analysis is to evaluate the efficacy and safety of erenumab in Japanese subjects with EM or CM, compared to placebo during the DBTP. The primary analysis will be performed when all randomized subjects have completed the week-24/ET assessments during the DBTP, and all data are collected for the primary endpoint. **All efficacy and safety data during DBTP will be cleaned and locked for the primary analysis. At the time of the primary analysis,** the individual randomization treatment assignment will be unblinded to selected staff of the sponsor conducting the analysis. Study subjects, investigators, and remaining sponsor staff will remain blinded to the original DBTP randomization treatment assignment until study completion.

7.2 Final Analysis

The objective of the final analysis is to evaluate the long-term profile of efficacy and safety of erenumab in Japanese subjects with migraine during the OLTP. The final analysis will be performed based on the final cleaned and locked data after all subjects have completed safety follow-up at the end of the study. Efficacy data and safety data from the OLTP will be tabulated by double-blind treatment group. No formal testing will be conducted.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database as well as eDiary data, PK, antibody, [REDACTED] and lab data outside of RAVE database.

8.3 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of causes. In general, data could be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, most of the efficacy endpoints are clinical outcome assessments (COAs) collected via daily eDiary or monthly assessments at the office visits. Missing COAs with respect to quality-of-life questionnaires [REDACTED] will not be imputed.

Subjects could miss entering several days of data in eDiary within each monthly interval. The calculation of monthly measurements about subjects' migraine and non-migraine headaches will be handled using the following method, also described in [Section 5.1.1](#).

- For each monthly interval with ≥ 14 days of eDiary use:
 - Monthly frequency measurements will be prorated to 28-day equivalents. Prorated result does not need to be rounded.
- [REDACTED]
- For monthly intervals with < 14 days of eDiary use, all monthly measurements will be set as missing.

Missing safety endpoints will not be imputed. Missing or incomplete dates will be listed as reported, except for incomplete start date of an adverse event or concomitant medication, which will be imputed as follows:

Missing	Imputation	Exception on adverse event start date
Day	01	Default to study day 1 if an adverse event started the same year and month as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events eCRF
Day/Month	01 JAN	Default to study day 1 if an adverse event started the same year as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events eCRF
Day/Month/Year	None	-

8.3.1 Missing Baseline Evaluation

Missing baseline evaluations will not be imputed.

All subjects included in the efficacy analysis set will have baseline monthly frequency or monthly average of migraine and non-migraine headaches related measurements after applying proration rule defined in [Section 8.3](#) since only subject with $\geq 80\%$ compliance of eDiary use during baseline will be eligible for randomization.

8.3.2 Missing Post-baseline Evaluation in Double-blind Treatment Period

Primary analysis of efficacy endpoints during the DBTP will be conducted using the repeated measures linear mixed effects model including both on-treatment and off-treatment observed data without imputation.

For the descriptive summary of mean monthly value calculated using the monthly value from each of months 4, 5, and 6 of the DBTP, if a subject has at least one monthly value at months 4, 5, and 6, then the subject contributes to the summary statistics.

In the sensitivity analysis on primary and secondary efficacy endpoints during the DBTP, missing continuous efficacy endpoints will be handled using last observation carried forward (LOCF) method, multiple imputation (MI) with assumption of missing at random (MAR) and missing not at random (MNAR) (with control-based pattern imputation). In those imputation methods, the mean over last 3 months of DBTP will be calculated based on imputed monthly values over month 4, 5 and 6.

In LOCF method, post-baseline missing continuous efficacy endpoints during DBTP will be imputed using the last observed value including baseline value.

Non-responder imputation (NRI) method will be applied to post-baseline missing dichotomous efficacy endpoint (eg, responder [Yes/No] based on $\geq 50\%$ reduction from baseline in monthly migraine days) during DBTP.

If the proportion of missing data in primary endpoint is high (eg, $> 20\%$ for primary analysis at week 24), further analysis will be performed to

- examine the frequency and reason of missing data
- determine if there are any patterns in the missing data
- distinguish true missing values from other unknown values (eg, due to measurement or sample processing error)

8.4 Detection of Bias

This study has been designed to minimize potential bias by allocating treatment groups randomly, assessing endpoints and handling withdrawals without knowledge of the treatment. Other factors that may bias the results of the study include:

- important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- inadvertent breaking of the blind before formal unblinding
- investigational product dosing non-compliance
- the timing of and reasons for early withdrawal from treatment and from study

The incidence of these factors may be assessed. Important protocol deviations will be listed and/or tabulated in the clinical study report (CSR). If necessary, the incidence of other factors will be tabulated.

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR.

The timing of and reasons for early withdrawal from treatment and from study will be tabulated and/or listed.

8.5 Outliers

Histograms will be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables.

Outliers due to data entry errors will be corrected by the study team before database lock. The validity of any questionable values or outliers will be confirmed. Outliers or any questionable values with confirmed validity will be included in the analyses.

However, ad-hoc sensitivity analyses may be conducted to evaluate the influence of extreme values in the data.

8.6 Distributional Characteristics

Continuous endpoints of change from baseline value will be analyzed under normality assumption. If they deviate appreciably from normality, appropriate transformations or the non-parametric alternatives such as Quade test ([Quade D, 1966](#)) may additionally be considered.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or higher.

9. Statistical Methods of Analysis

9.1 General Considerations

The primary objective of this study is to evaluate the effect of erenumab 70 mg QM compared to placebo on the change from baseline in mean MMD over months 4, 5, and 6, in subjects with EM or CM.

Summary descriptive statistics by each treatment group will be tabulated at each visit or by treatment period. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, SDs, SEs, first and third quartiles, and minimums and maximums. For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

Change from baseline for efficacy endpoints during the DBTP or OLTP will be summarized using the study baseline.

Primary analysis for continuous efficacy endpoints during the DBTP will be based on a linear mixed effects model including appropriate terms and covariates in the model. Nominal p-value will be provided for the comparison between erenumab 70 mg vs. placebo for efficacy endpoints. The adjusted mean change from baseline for each treatment group, and the adjusted treatment difference compared to placebo, associated 95% confidence intervals, and p-value for treatment comparison will be reported. Primary analysis for dichotomous efficacy endpoints during the DBTP will be based on the stratified Cochran-Mantel-Haenszel (CMH) test. Adjusted odds ratio compared to placebo, associated 95% confidence intervals, and p-value will be reported.

Analysis for efficacy endpoints during the OLTP will be descriptive.

9.2 Subject Accountability

For the primary analysis at week 24, the disposition of all enrolled subjects will be tabulated by the randomized treatment group. The summary will include the number of subjects who are randomized, the number and percent of subjects who receive the double-blind IP, who complete double-blind IP, discontinue double-blind IP and reasons

for discontinuing, who complete the 24-week DBTP, and who withdraw prematurely from the study before completion of the 24-week DBTP and their reasons for withdrawal.

For the final analysis, disposition of the OLTP and the entire study will be tabulated, which include the number and percent of subjects who enter the OLTP, who receive erenumab 70 mg, who complete erenumab 70 mg, discontinue erenumab 70 mg and reasons for discontinuing, who complete the OLTP, who complete the study, and who withdraw prematurely from the study and their reasons for withdrawal.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. IPDs will be summarized and listed by randomized treatment group.

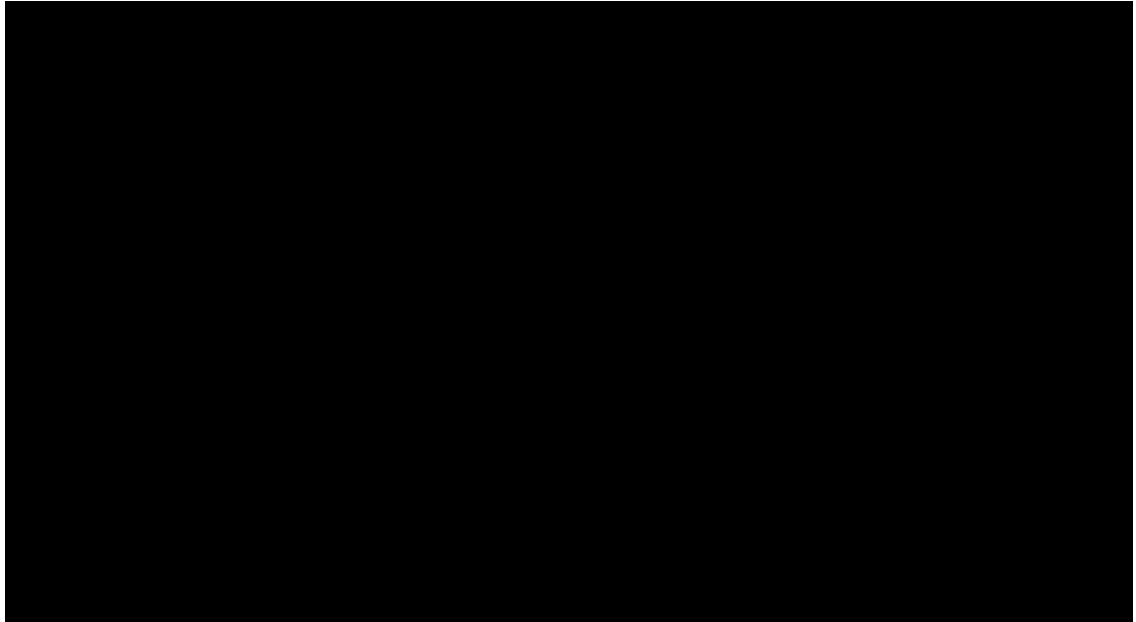
9.4 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics by randomized treatment group and overall study population using FAS. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Age group (< median vs. ≥ median)
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI, kg/m²)
- Targeted neurological disease diagnosis at baseline
- Disease duration of migraine with or without aura (years)
- Age at onset of migraine
- Summary of prior migraine preventive treatment and reasons for discontinuation
- Summary of current migraine preventive treatment at baseline

- Acute headache medication used during baseline period:
 - a) Migraine-specific
 - b) Non-migraine-specific
- Stratification factors, including EM/CM and migraine preventive treatment status (ever used [prior and/or current] or never used)
- Monthly migraine days during baseline period



9.5 Efficacy Analyses

The primary analysis of efficacy endpoints will utilize the efficacy analysis set. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study.

For primary analysis at week 24, the continuous change from baseline efficacy endpoints as specified in [Section 5.4.2](#) will be analyzed using linear mixed effect models adjusted by stratification factors and baseline value including both on-treatment and off-treatment observed data as the primary analysis method. The dichotomous efficacy endpoints will be analyzed using the stratified CMH test adjusted by stratification factors after the missing data are imputed as non-response.

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
<p>Change from baseline in mean monthly migraine days (MMD) over months 4, 5, and 6</p> <p><i>(Note: Result at each timepoint during DBTP will also be generated in the same model.)</i></p>	<ol style="list-style-type: none"> Summary statistics of observed MMD and change from baseline in MMD by visit during DBTP, and mean MMD over months 4, 5, and 6 Least squares mean at each timepoint during DBTP from a linear mixed effect model adjusted by stratification variables and baseline value using observed data Test treatment difference between erenumab 70 mg and placebo using a contrast from the model in #2. 	<ol style="list-style-type: none"> LOCF: Summary statistics and analyze using an ANCOVA model for the mean MMD over months 4, 5, and 6. MI with MAR assumption MI with MNAR assumption (control-based pattern imputation). The interaction of treatment group by stratification factor will be tested with significant level of 0.15. If the interaction term is significant, the interaction term will be included in the model as sensitivity analysis for the primary analysis method.

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis
Response defined as at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6 <i>(Note: Result at each timepoint during DBTP will also be generated in the same model.)</i>	<ol style="list-style-type: none"> Summary statistics by visit using observed data, and responder rate calculated using mean MMD over months 4, 5, and 6 A stratified Cochran-Mantel-Haenszel (CMH) test adjusted by stratification variables will be used after the missing data are imputed as non-response 	<ol style="list-style-type: none"> Without imputation, adjusted odds ratios by visit from a generalized linear mixed model adjusted by stratification variables and baseline MMD using observed data, and adjusted odds ratio for mean over months 4, 5 and 6 from the same generalized linear mixed model using a contrast. NRI, adjusted odds ratio for $\geq 50\%$ MMD responder rate with respect to mean MMD over months 4, 5, and 6 from a logistic regression model adjusted by stratification variables and baseline MMD Breslow-Day test will be conducted to test the homogeneity of the odds ratios across the stratification factors.
Change from baseline in mean monthly acute migraine-specific medication days over months 4, 5, and 6 <i>(Note: Result at each timepoint during DBTP will also be generated in the same model.)</i>	<ol style="list-style-type: none"> Summary statistics of observed data and change from baseline values by visit during DBTP and mean monthly acute migraine-specific medication days over months 4, 5, and 6 Least squares mean at each timepoint during DBTP from a linear mixed effect model adjusted by stratification variables and baseline value using observed data Test treatment difference between erenumab 70 mg and placebo using a contrast from the model in #2. 	<ol style="list-style-type: none"> LOCF: Summary statistics and analyze using an ANCOVA model for the mean monthly acute migraine-specific medication days over months 4, 5, and 6. MI with MAR assumption MI with MNAR assumption (control-based pattern imputation). The interaction of treatment group by stratification variable will be tested with significant level of 0.15. If the interaction term is significant, the interaction term will be included in the model as sensitivity analysis for the primary analysis method.

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method (Specify Analysis Set if FAS is Not Used)	Sensitivity Analysis

9.5.1 Analyses of Primary and Secondary Efficacy Endpoints

For the primary analyses at the end of DBTP, the continuous primary and secondary endpoints will be tested using a linear mixed model based on observed monthly data from 24-week DBTP with appropriate contrasts for treatment comparison for the corresponding efficacy endpoints: change from baseline in mean monthly values over months 4, 5, and 6.

The model will include treatment, visit, treatment by visit interaction, stratification factors, and baseline value as covariates. If applicable, the first-order autoregressive covariance structure is assumed. Least-squares means (LSMs) for each treatment group, standard errors, associated 95% confidence intervals, difference of LSMs compared to placebo group, associated 95% confidence intervals and unadjusted two-sided p-values will be tabulated by visit and treatment, as well as for the mean monthly values over months 4, 5, and 6 in DBTP.

For dichotomous efficacy endpoints during the DBTP, adjusted odds ratios compared to placebo group, associated 95% confidence intervals and unadjusted two-sided p-values will be tabulated by visit and treatment.

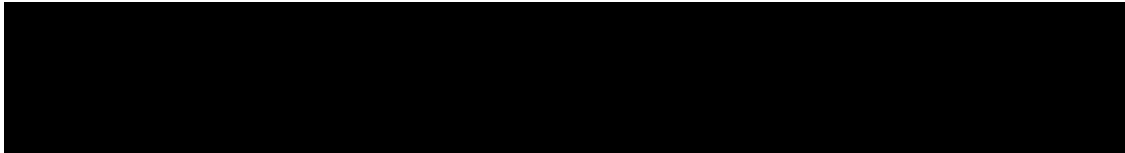
Sensitivity analyses described below will be performed for the primary and secondary endpoints:

1. Summary statistics and ANCOVA model for continuous endpoints (logistic regression model for dichotomous endpoints) using imputed data by LOCF (NRI for binary endpoint). Treatment, baseline value and stratification variables will be included in the model.
2. Odds ratio estimated from a generalized linear mixed model including treatment group, stratification variables, scheduled visit, interaction of treatment and scheduled visit and baseline value using observed data for dichotomous endpoint.
3. MI with assumption of MAR and MNAR (control-based pattern imputation) for continuous endpoints.
4. Primary summary and analysis by the subgroup (see [Section 4.2](#)) of
 - EM vs. CM
 - Prior migraine preventive treatment status (ever used [prior and/or current] or never used)
 - Prior migraine preventive treatment failure status (failed vs non-failed [including never used])
 - BMI (< median vs. ≥ median)
 - Body weight (< median vs. ≥ median)

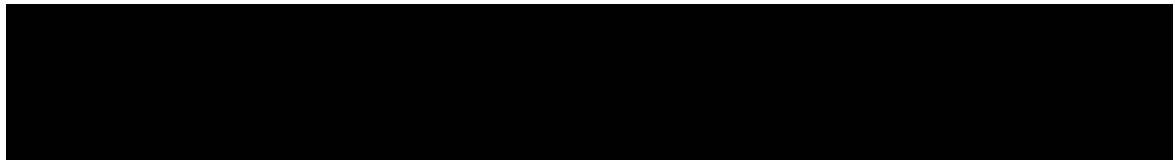
5. **Primary summary and analysis method with treatment and stratification interaction for continuous endpoints: the interaction of treatment group by stratification factor will be tested with significant level of 0.15. If the interaction term is significant, the interaction term will be included in the model as sensitivity analysis for the primary analysis method. For dichotomous endpoint with CMH test as the primary analysis method, Breslow-Day test will be conducted to test the homogeneity of the odds ratios across the strata.**

The purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Subgroup analyses are performed for primary and secondary efficacy endpoints using the same method as Primary Summary and Analysis Method but performed within each described subgroup.

9.5.2 Analyses of Exploratory Efficacy Endpoints in Double-blind Treatment Period



9.5.3 Analyses of Exploratory Efficacy Endpoints in Open-label Treatment Period



9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoints

For safety endpoints, all randomized subjects who received at least one dose of investigational product (ie, Safety Analysis Set) will be analyzed based on the randomized treatment unless a subject has received the incorrect dose during the entire period of interest (treatment period or study).

For safety analyses of non-AE data in OLTP, descriptive summaries will be tabulated based on observed data using pre-OLTP baseline.

No statistical testing comparing treatment groups will be performed in the safety analyses.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later will be used to code all adverse events (AEs) to a system organ class (SOC) and a preferred

term (PT). All AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All AE summary tables described below will be summarized by treatment group using subject incidence for the DBTP and be repeated using both subject incidence and exposure-adjusted subject incidence for the OLTP.

The subject incidence of AEs will be summarized for all treatment-emergent adverse events (TEAEs), serious AEs, AEs leading to withdrawal of investigational product, fatal AEs, **device-related AEs**, and adverse events of interest (EOI) including

- Ischaemic Central Nervous System Vascular Conditions SMQ (Narrow)
- Ischaemic Heart Disease SMQ (Narrow and Broad)
- Peripheral Arterial Disease AMQ (Narrow)
- Hypertension SMQ (Narrow and Broad)
- Constipation AMQ (Narrow and Broad)
- Alopecias AMQ (**Broad**)

Subject incidence of all TEAEs, SAEs, AEs leading to withdrawal of investigational product, and fatal AEs will be tabulated by SOC in alphabetical order and PT in descending order of frequency.

Subject incidence of EOI (standardized MedDRA queries [SMQ] and/or Amgen medical queries [AMQ]) will also be summarized according to their categories and PT in descending order of frequency.

In addition, **summary** of all TEAEs occurring in at least 3% of the subjects **during DBTP** by PT in any treatment arm will be provided in descending order of frequency.

Summaries of all TEAEs and SAEs will be tabulated by SOC, PT, and grade.

9.6.3 Laboratory Test Results

Summary of change from baseline for alanine transaminase (ALT) and aspartate aminotransferase (AST) will also be provided by visit for the DBTP (use study baseline to calculate change from baseline) and for OLTP (use pre-OLTP baseline to calculate change from baseline).

Subject incidence of liver function test abnormalities (including AST, ALT, Total Bilirubin [TBL] and Alkaline Phosphatase [ALP]) will also be summarized by treatment group and treatment period.

9.6.4 Vital Signs

The analyses of vital signs (systolic/diastolic blood pressure [SBP/DBP] and heart rate [HR]) will include summary statistics of change from baseline over time by treatment group.

Subject incidence at each time-point within the following defined categories for each treatment period:

- **Increase from baseline ≥ 20 mmHg in SBP with SBP > 140 mmHg**
- **Increase from baseline ≥ 20 mmHg in SBP with SBP ≤ 140 mmHg**
- **Increase from baseline ≥ 10 mmHg in DBP with DBP > 90 mmHg**
- **Increase from baseline ≥ 10 mmHg in DBP with DBP ≤ 90 mmHg**
- Change from baseline in **HR** of ≥ 15 bpm (increase) or **HR** ≥ 120 bpm
- Change from baseline in **HR** of ≤ -15 bpm (decrease) or **HR** ≤ 50 bpm

9.6.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The number and percentage of subjects reporting any suicidal ideation and any suicidal behavior will be summarized descriptively by treatment group separately for the DBTP and OLTP. Shift table of C-SSRS maximum severity of suicidal ideation/behavior compared to baseline will be provided by treatment group separately for the DBTP and OLTP.

9.6.6 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

Subject incidence of abnormal ECG diagnosis will be summarized by treatment group separately for the DBTP and OLTP.

9.6.7 Beck Depression Inventory (BDI)-II

The number and percentage of subjects in each severity grade of depression will be summarized descriptively at baseline and week 24 by treatment group. Shift of BDI-II severity grade of depression at week 24 compared to baseline will be provided by treatment group.

9.6.8 Antibody Formation

The number and percentage of subjects who develop anti-erenumab antibodies (binding and, if positive, neutralizing) will be tabulated by treatment group for the entire study.

The list of subjects with positive antibodies at any time will be provided.

In addition, a listing of treatment-emergent AEs will be provided for subjects with positive binding or neutralizing antibodies.

9.6.9 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group and by study period. The number and percentage of subjects with dose change, reason for dose change and duration of exposure to investigational product in days will be summarized by treatment group.

9.6.10 Exposure to Concomitant Medication

The number and proportion of subjects receiving acute headache medications will be summarized by acute headache medication category for each treatment group.

10. Changes From Protocol-specified Analyses

The scope of the primary analysis will include efficacy and safety data during DBPT only (see [Section 7.1](#)).

11. Literature Citations / References

Quade, D. (1966), Rank analysis of covariance, University of North Carolina, Institute of Statistics Mimeo Series. No. 483

Silberstein SD, Marmura MJ, Shaw J, et al. Headache prophylaxis with BoNRA: patient characteristics. *Headache*. 2010;40:63-70.

12. Data Not Covered by This Plan

There are no plans to specifically analyze or summarize the following data points.

- ECG interval data
- PK
- Data from [REDACTED]
- Data for [REDACTED]
- **Data from optional interview-based substudy per Protocol Amendment 2**

13. Appendices

Appendix A. Reference Values/Toxicity Grades

Adverse event severity and laboratory toxicity are graded based on NCI Common Toxicity Criteria version 4.03, which is available at the following:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf